***274270** Links

DIHYDROPYRIMIDINE DEHYDROGENASE; DPYD

Alternative titles; symbols

DPD
DIHYDROPYRIMIDINURIA; DHP
THYMINE-URACILURIA, HEREDITARY, INCLUDED
DIHYDROPYRIMIDINE DEHYDROGENASE DEFICIENCY, INCLUDED
DPD DEFICIENCY, INCLUDED
PYRIMIDINEMIA, FAMILIAL, INCLUDED
5-@FLUOROURACIL TOXICITY, INCLUDED

Gene map locus 1p22

TEXT

Dihydropyrimidine dehydrogenase (DPD, or DPYD; EC 1.3.1.2) is the initial and rate-limiting enzyme in the 3-step pathway of uracil and thymidine catabolism and in the pathway leading to the formation of beta-alanine. Berger et al. (1984) presented findings in 3 unrelated patients (2 boys and 1 girl) with a nonspecific clinical picture of cerebral dysfunction and persistent urinary excretion of excessive amounts of uracil, thymine, and 5-hydroxymethyluracil. The excretory pattern suggested deficiency of DPD. Autosomal recessive inheritance was supported by the finding that the parents of 1 patient were first cousins. DPD is also the principal enzyme involved in the degradation of the chemotherapeutic drug 5-fluorouracil (5-FU), which acts by inhibiting thymidylate synthase (188350).

Wadman et al. (1984) postulated deficiency of DPD as the cause of the thymine-uraciluria they observed in a child with autism. This is an example of a pharmacogenetic condition of the pharmacokinetic variety, pharmacodynamic being the other main category.

Tuchman et al. (1985) described a 27-year-old woman who suffered an unusually severe reaction to 5-FU given in limited dosage on a weekly schedule. Symptoms included stomatitis, leukopenia, thrombocytopenia, hair loss, diarrhea, fever, marked weight loss, cerebellar ataxia, and neurologic symptoms, progressing to semicoma. High levels of uracil and thymine were found in the urine of the patient and of one brother; both had very high plasma and urinary concentrations of pyrimidine bases. Serum levels and urinary excretion of uric acid were normal in all members of the family, and the patient's white cell thymidine kinase was normal. The mother's urine showed a small amount of uracil but no thymine. A second brother and a sister showed none of the abnormalities. The authors suggested that the defect may be in dihydropyrimidine dehydrogenase which is involved in pyrimidine base

degradation. The defect would not be expected to be apparent clinically unless the subject is given a pyrimidine-base analog. Deficiency of DPD in fibroblasts from patients with thymine-uraciluria was described by Berglund et al. (1979) in a child with medulloblastoma and by Bakkeren et al. (1984).

Diasio et al. (1988) established autosomal recessive inheritance by describing consanguinity in the parents of a homozygote and partial deficiency of DPD in both of her children. The proband, a previously completely healthy 40-year-old woman, suffered severe neurotoxicity due to 5-fluorouracil given for breast cancer. Diasio et al. (1988) found that after administration of a 'test' dose of 5-fluorouracil to this patient, a markedly prolonged elimination half-life (159 min) was observed with no evidence of catabolites of the drug in plasma or cerebrospinal fluid and with 89.7% of the administered dose being excreted into the urine as unchanged drug. Partial deficiency of the enzyme was found also in the patient's father; the mother was deceased. The enzyme was assayed in peripheral blood mononuclear cells.

Brockstedt et al. (1990) commented that 7 of the 8 previously reported pediatric patients were Dutch. They reported a ninth pediatric case. Van Gennip et al. (1994) described a Dutch family in which 1 individual was hospitalized at the age of 25 months with bilateral microphthalmia, coloboma of the iris and choroid, nystagmus, and a gradually increasing psychomotor retardation. The patient was found to be homozygous for a deletion of an exon of 165 nucleotides (274270.0001), whereas both parents and 1 sib were heterozygous.

DPD deficiency is a clinically heterogeneous disorder. Vreken et al. (1997) stated that patients with a nearly complete enzyme defect show convulsive disorders in about 50% of cases, whereas patients experiencing acute 5-fluorouracil toxicity usually show DPD enzymatic activities in the heterozygous range. Vreken et al. (1997) found a 4-bp deletion in the DPYD gene (274270.0003) in a Dutch consanguineous family with DPD deficiency.

To evaluate the prevalence of dihydropyrimidinuria (DHPuria), Sumi et al. (1998) analyzed urine samples from 21,200 healthy Japanese infants and found 2 cases of DHPuria without clinical symptoms. Based on this result, they estimated the prevalence to be approximately 1 in 10,000 births in Japan. In addition, they analyzed pyrimidine catabolism on a previously reported family with an adult DHPuria case (Sumi et al., 1996; Hayashi et al., 1996). In this patient, Hayashi et al. (1996) had demonstrated metabolic changes predicting a risk of severe 5-fluorouracil toxicity. On restudy of the family of this patient, a sister of the proband was found to excrete large amounts of dihydrouracil and dihydrothymine. The parents and the child of the propositus showed slight increases of dihydrouracil and dihydrothymine. This was the first reported instance of a family with 2 cases of DHPuria. To determine the inheritance of DHPuria in this family and to examine the risk of 5-FU toxicity, a uracil loading test was performed on the parents. Urinary dihydrouracil concentrations in the parents after the loading was several times higher than those in normal control persons, the finding being consistent with DHPuria heterozygotes. Sumi et al. (1998) concluded that DHPuria is an autosomal recessive condition. Sumi et al. (1998) suggested that homozygotes may have a high risk of 5-FU toxicity, while the risk may be relatively low in heterozygotes.

Yokota et al. (1994) cloned and sequenced pig and human DPD cDNAs. The pig and human enzymes contain 1,025 amino acids and have a calculated molecular mass of 111,416 and 111,398, respectively. The sequence of the gene suggested that DPD has at least 3 distinct domains. Using somatic cell hybrid strategies, Yokota et al. (1994) mapped the gene for DPD, symbolized DPYD, to the centromeric region of human chromosome 1 between 1p22 and 1q21. By fluorescence in situ hybridization, Takai et al. (1994) assigned the DPYD gene to 1p22.

Great phenotypic variability had been observed with DPD deficiency, with convulsive disorders, motor retardation, and mental retardation being the most frequent manifestations. Van Kuilenburg et al. (1999) could establish no clear correlation between genotype and phenotype in a review of 17 families presenting 22 patients with complete deficiency of DPD. In this group of patients, 7 different mutations were identified, including 2 deletions, 1 splice site mutation, and 4 missense mutations. The most common mutation by far, accounting for 52% of mutant alleles, was the G-to-A transition at the first nucleotide of the splice donor site of intron 14, IVS14+1G-A (274270.0001), leading to deletion of exon 14.

Van Kuilenburg et al. (1999) studied the expression of DPD in various blood cell components. They demonstrated that the highest level of DPD was found in monocytes followed by that of lymphocytes, granulocytes, and platelets, whereas no significant activity of DPD could be detected in erythrocytes. The activity of DPD in peripheral blood mononuclear cells was intermediate between that observed in monocytes and lymphocytes. The mean percentage of monocytes in PBM cells obtained from cancer patients proved to be significantly higher than that observed in PBM cells from healthy volunteers. Van Kuilenburg et al. (1999) also observed a profound positive correlation between the DPD activity of PBM cells and the percentage of monocytes, thus introducing a large inter- and intrapatient variability in the activity of DPD and hindering the detection of patients with a partial DPD deficiency.

Of 53 cases of DPD deficiency associated with 5-FU-related toxicity reviewed by Milano et al. (1999), 19 cases had moderate or marked DPD deficiency (less than 70% of the mean population value). More of the cases occurred in women (15 of 19), which was in accord with several previous reports Milano et al. (1992). The toxicity score was significantly higher in patients with markedly low DPD. None of the reported cases, however, had complete DPD deficiency, even in the 2 patients that died. Neurotoxicity was a predominant manifestation when DPD deficiency was marked. Cardiotoxicity was observed in only 1 case.

NOMENCLATURE

To standardize DPYD allele nomenclature and to conform with the international human gene nomenclature guidelines, McLeod et al. (1998) described an alternative to the existing arbitrary system. Based on recommendations for human genome nomenclature, they proposed that each distinct allele be designed by DPYD followed by an asterisk and an arabic numeral. Criteria for classification as a distinct allele were also presented.

ALLELIC VARIANTS
(selected examples)

.0001 DIHYDROPYRIMIDINE DEHYDROGENASE DEFICIENCY [DPYD, 165-BP DEL, IVS14, G-A, +1]

THYMINE-URACILURIA
5-@FLUOROURACIL TOXICITY

Meinsma et al. (1995) determined the molecular basis of thymine-uraciluria by studying the phenotype and genotype of a family of a patient showing no DPD activity. Fibroblast mRNAs from the patient and 4 family members were subjected to RT-PCR using primers generated from the human DPYD cDNA sequence. In the patient, DPYD mRNA was found to lack a segment of 165 nucleotides as a result of exon skipping. In the parents and 1 sib, DPYD mRNA was found to be heterozygous for the deletion,

while a brother had only normal transcript. The deficient patient had no detectable DPD protein. The precise nature of the presumed splicing defect was not identified. The homozygous proband, who was first described by van Gennip et al. (1994), had been admitted to hospital at the age of 25 months with bilateral microphthalmia, coloboma of the iris and choroid, nystagmus, and a gradually increasing psychomotor retardation. No growth retardation or neurologic abnormalities were detected. All other members of the pedigree were healthy and showed no ocular abnormalities.

Wei et al. (1996) found the same 165-nucleotide deletion in an unrelated British family having a cancer patient with partial DPD deficiency and severe toxicity after 5-fluorouracil treatment. They found that a G-to-A point mutation within the 5-prime splicing site (GT to AT), which appeared to cause exon skipping, resulted in an inactive DPYD allele.

Independently, Vreken et al. (1996) showed that the 165-nucleotide deletion in the mature DPD mRNA was due to a G-to-A transition in the invariant GT dinucleotide splice donor site downstream of the skipped exon. The same mutation was identified in another, unrelated, Dutch patient. Because this mutation destroyed a unique MaeII restriction site, rapid screening was possible using restriction enzyme cleavage of the amplified genomic region encompassing this mutation. Analysis of 50 controls revealed no individuals heterozygous for the mutation. Although both patients had psychomotor retardation, the other features were different. The second patient presented with convulsions and had no ocular manifestations and no microcephaly.

Van Kuilenburg et al. (1997) described another patient with severe 5-fluorouracil-related toxicity and heterozygosity for the same G-to-A splice site mutation with a deletion of 165 basepairs. They stated that the G-to-A mutation had been found in 8 of 11 patients suffering from complete deficiency of the enzyme. Hyperpigmentation and cardiotoxicity were observed as side effects of 5-fluorouracil in this patient. The enzyme activity in leukocytes of the patient proved to be in the heterozygous range. The 11 patients with complete deficiency had homozygosity of the G-to-A mutation. The patients came from Denmark, Finland, and the Netherlands.

Vreken et al. (1998) stated that the deletion of exon 14 due to the G-to-A mutation had been identified in 22 of 42 alleles from patients with complete DPD deficiency.

Van Kuilenburg et al. (1999) found that the IVS14+1G-A mutation, leading to deletion of exon 14 of the DPYD gene, accounted for 23 of 44 (52%) of DPD deficiency alleles.

.0002 5-@FLUOROURACIL TOXICITY [DPYD, ASP974VAL]

In a patient who experienced severe 5-fluorouracil-related toxicity, Harris et al. (1991) and Albin et al. (1995) found a point mutation at codon 974 of the DPYD gene resulting in the substitution asp974 to val. The aspartic acid residue at codon 974 is not within the putative catalytic sites of the protein and the amino acid is conserved in the human, pig, and cow sequences. Ridge et al. (1997) studied the frequency of this mutation in 29 Scottish subjects with low DPD enzyme activity and in 274 American subjects. They detected no mutations in the 606 alleles studied and concluded that mutations at codon 974 are a rare event.

Ridge et al. (1997) studied the frequency of asp974 to val in 29 Scottish subjects with low DPD enzyme activity and in 274 American subjects. They detected no mutations in the 606 alleles studied and concluded that mutations at codon 974 are a rare event.

.0003 DIHYDROPYRIMIDINE DEHYDROGENASE DEFICIENCY [DPYD, 4-BP DEL, 296TCAT]

In a Dutch consanguineous family with dihydropyrimidine dehydrogenase deficiency, Vreken et al. (1997) found deletion of nucleotides 296 to 299 (TCAT) leading to premature termination of translation. The deletion was located in a TCAT tandem-repeat sequence and most likely resulted from unequal crossing over or slipped mispairing. Three homozygous individuals were identified in the family. Two of these showed convulsive disorders but 1 was clinically normal. No clear correlation between DPYD genotype and phenotype was possible.

.0004 DIHYDROPYRIMIDINE DEHYDROGENASE DEFICIENCY [DPYD, CYS29ARG]

Vreken et al. (1997) described 2 new patients who were both compound heterozygotes for the cysteine-to-arginine (C29R) and the common splice donor site mutation (274270.0001). Only one of these patients showed convulsive disorder during childhood, whereas the other showed no clinical phenotype, further illustrating the lack of correlation between genotype and phenotype in DPD deficiency.

Vreken et al. (1997) described another patient who was a compound heterozygote for C29R and arg886 to his (R886H; 274270.0006). The patient had been hospitalized for upper airway infection and was being investigated for unexplained hypokalemia. The patient showed no convulsions or other neurologic abnormalities. By assaying recombinant C29R mutant enzyme, they found that C29R had no detectable DPYD activity; however, R886H showed activity about 40% of normal.

.0005 DIHYDROPYRIMIDINE DEHYDROGENASE DEFICIENCY [DPYD, 1-BP DEL, 1897C]

Vreken et al. (1997) described a frameshift mutation due to deletion of 1897C in the DPYD gene in a child with DPD deficiency. He was the offspring of first-cousin parents; an earlier-born child had died before her first birthday with severe neuromotor retardation and febrile convulsions. At the age of 9 months the patient showed febrile convulsions, severe neuromotor retardation, and spastic tetraplegia. Cerebral MRI showed ventriculomegaly with white matter hypodensity. At the age of 6 years, thymine-uraciluria was noted and DPD deficiency in fibroblasts demonstrated. Surprisingly, the father of the patient was also completely DPD deficient, although he had no history of convulsions. The mother of the patient showed intermediate DPD activity consistent with obligate carrier status. The patient was heterozygous for this 1-bp deletion, whereas the father was thought to be homozygous. The nature of the heterozygous mutation carried by the mother and transmitted to the son was not determined.

.0006 DIHYDROPYRIMIDINE DEHYDROGENASE DEFICIENCY [DPYD, ARG886HIS]

Vreken et al. (1997) described compound homozygosity for 2 missense mutations in the DPYD gene in a patient in whom metabolic screening had demonstrated thymine-uraciluria. The patient had been hospitalized for upper airway infection and was being investigated for unexplained hypokalemia. The patient showed no convulsions or other neurologic abnormalities. Two missense mutations, 85T-C and 2758G-A, leading to amino acid substitutions, cys29 to arg (C29R; 274270.0004) and arg886 to his (R886H), respectively, were demonstrated. To determine the significance of these mutations, they were introduced separately into wildtype DPD cDNA and subcloned in an expression vector. Vreken et al. (1997) found that enzymatic activity of the mutant C29R was undetectable, whereas mutant R886H showed about 40% of the normal activity. They concluded that the C29R mutation is alone sufficient to explain the DPD-deficient phenotype and that the R886H mutation is probably a rare polymorphism.

SEE ALSO

Wadman et al. (1985); Wilcken et al. (1985)

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